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5 DR. KING: Hi, everybody. Thanks for
6 hanging in there for this long today. It's been a
7 really interesting conference so far. I'm humbled
8 to be here. I am not an ethicist or statistician.
9 I'm just going to talk about the development of a
10 MERS protocol that is hopefully going to happen in
11 the very near future.

12 Just about five or six weeks ago,
13 different representatives from HHS agencies went
14 to the Kingdom of Saudi Arabia to talk about MERS.
15 During that time, what I call the "master
16 protocol" or the "NIH protocol for Ebola" was
17 given to the Saudi Arabian FDA and the Ministry of
18 Health to look at. They were intrigued with it
19 enough to ask for more information, and it looks
20 like we're going to join as a partner with the
21 Kingdom of Saudi Arabia and do a MERS therapeutic
22 study.

1 In thinking about this, I've been
2 involved a long time with influenza trials, but it
3 was intriguing and it was intriguing to hear
4 information today about doing studies in new
5 emerging diseases, and what the thought process
6 should be behind that. Dr. Hoke, I think, gave
7 some very interesting ideas, some of which I'm
8 going to present here.

9 I wanted to start thinking through some
10 of the logical steps to design as possibly good
11 trial as I could. The outline of that is on this
12 slide, look at the pathogenesis of the virus. I
13 think it's critical to know the epidemiology as
14 best you can to decide what kind of trial to do.

15 Know the treatment options. In this
16 case, we don't have anything yet for MERS. There
17 are things that are evolving. We really don't
18 have any human data right now.

19 The clinical study logistics, like what
20 sites to use, what the population is you want to
21 focus on. I think diagnostics is going to be
22 critical here. I think it would really be ideal

1 for each site that's going to participate in this
2 study to have a very sensitive and rapid
3 diagnostic tool for the MERS CoV, in order to
4 enroll people quickly, to get intervention
5 quickly, and to not enroll people who do not have
6 MERS.

7 Because of time, I'm going to go rapidly
8 behind that progression and get to the design of
9 the trial. First, MERS CoV belongs to the family,
10 Coronaviridae, its cousins are SARS and human
11 coronavirus, natural respiratory infections, which
12 are not that severe.

13 The virus binds to dipeptidyl peptidase
14 4, or DDP4 receptor, which is present in high
15 density in the human lung, so it's not surprising
16 that the primary manifestation is respiratory
17 disease, and it is often very severe and leads to
18 massive respiratory failure, then subsequent organ
19 failure.

20 The geographical spread of MERS CoV, at
21 least we have some information over the last three
22 going on four years, which I think is helpful in

1 talking about where to do this study. It was
2 first detected in the Arabian Peninsula in 2012,
3 and then each subsequent year, the footprint of
4 this disease has spread until this past year,
5 there's been at least 26 countries that have had
6 MERS cases. Most of those are from travelers from
7 the Arabian Peninsula.

8 The red dots on this slide represent the
9 number of cases in that country that year. It's
10 very clear that Saudi Arabia has the most cases.
11 If you want to do a study, you want to do it in
12 Saudi Arabia.

13 A little bit more about EPI. As of a
14 little over a week ago, there has been 1,611
15 laboratory confirmed MERS cases, with 575 deaths,
16 or 37 percent case fatality. Specific to Saudi
17 Arabia during the same time, there has been 1,273
18 cases, which is a whopping almost 80 percent of
19 the global cases. They have had 542 deaths with
20 43 percent case fatality rate.

21 Over the last couple of years, there has
22 been a seasonable pattern to the MERS CoV where at

1 least in the Arabian Peninsula, you have a surge
2 in the spring time, April to May, with a lesser
3 surge but measurable in September to November.
4 This past year was no exception.

5 If you're going to do a study, you might
6 want to aim to the periods of time when you are
7 going to have outbreaks, just like Dr. Hoke
8 mentioned.

9 The main risk factors for contracting
10 MERS is age. The median age in one study was 62
11 years, and definitely most of the cases are above
12 50, particularly the severe ones. It's male
13 predominant. Two-thirds of the cases have been
14 male. Over 80 percent of those individuals at
15 least with severe disease had comorbid conditions,
16 especially diabetes.

17 Being a health care worker is a big
18 factor for risk, although the health care workers
19 seem to have a little bit less severe disease than
20 the primary.

21 In thinking about endpoints, which I
22 think is critical in a study, and I'll bring in a

1 little bit of the ethics here, I think it's
2 important to consider doing a trial where you
3 really don't have a lot of experience with the
4 pharmaceutical, to pick more severe disease. Then
5 the risk/benefit ratio, I think, favors in having
6 a less studied drug.

7 Some of the things I've looked at is the
8 outcome rates and the median time from onset of
9 symptoms. For hospitalized individuals, it's 91
10 percent of the cases are hospitalized, and usually
11 around four days after onset of symptoms,
12 pneumonia, 90 percent, and they usually developed
13 pneumonia within a week. ICU admissions, and
14 those are hospitalized, up to 70 percent, and it's
15 usually about the sixth day after symptoms start.
16 Mechanical ventilation is 66 percent. These are
17 extremely high numbers for those who were
18 hospitalized, and around seven days is when they
19 have the onset of symptoms.

20 Finally, and I highlighted death because
21 that is right now what we are considering using
22 for the main endpoint, 60 percent of those who are

1 hospitalized in one publication died, and the time
2 of death was usually about 11 to 12 days from time
3 of symptoms.

4 I want to go into brief design of the
5 adaptive and flexible randomized control study. I
6 must say I copied this off the Ebola master
7 protocol. It's for severe MERS CoV illness. I
8 think it's really important to decide what's
9 severe. I think just getting hospitalized doesn't
10 mean it's severe. I think we need to come up with
11 criteria. Some examples have been used in flu
12 studies recently of more severe disease, and that
13 is if we require oxygen supplementation or signs
14 of respiratory distress.

15 Another thought is to use the new score,
16 that is the National Emergency Warning System,
17 scoring system, and it fits for respiratory
18 disease, where you are looking at vital signs and
19 oxygen saturation subjects, and assign a new score
20 high enough that you know you are enrolling severe
21 disease.

22 This study will be randomized. We chose

1 100 subjects per arm, based upon the incident rate
2 of death, which at the present time for
3 hospitalized patients is 60 percent, recognizing
4 that we had to follow this closely by the time we
5 start the study because the mortality rate may
6 drop, like what was seen for Ebola.

7 We also want to randomize by site
8 because -- as I will get into a little later,
9 we're going to use the standard of care as the so-
10 called placebo or control arm. We want to make
11 sure we can randomize on site to avoid biases in
12 different types of treatment and different types
13 of medical sites.

14 We want to use optimized standard of
15 care. I think it's important to have a steering
16 committee before a trial starts to identify what
17 that is and to use that as an SOP. I think that
18 is critical to have people, medical experts,
19 within Saudi Arabia, be part of that design of
20 standard of care.

21 When possible -- nobody has mentioned
22 this yet -- for the emerging disease, I think it

1 is important to try to blind the study, to have a
2 double blind study, but that may be really
3 difficult if you're trying to institute the trial
4 rapidly, and you may not have placebo controls,
5 pills, or I.V. preparations. That may be
6 difficult, but through our best efforts, we will
7 try to have this blinded.

8 It will be adaptive, meaning we can
9 introduce arms. You can either have just one arm
10 with standard of care, with a new experimental
11 agent, or put in multiple arms to include multiple
12 experimental agents. That just depends on what is
13 available.

14 Getting the idea in new emerging
15 diseases that there won't be a lot of drugs
16 available up front. I may be wrong, but I think
17 you are going to probably start out with a two arm
18 trial, but in the case where we have multiple
19 drugs, I think it's important to be able to adapt
20 to that and put them in at various time points
21 even.

22 We will have frequent interim

1 monitoring, both for safety and efficacy, and we
2 will monitor -- when we are looking for efficacy,
3 we might not have to get to 100 subjects per arm
4 to find an agent that has improved outcomes than
5 an optimized standard of care.

6 The aim is to find a candidate quickly,
7 and if it's a real emergency or if there's a real
8 big outbreak, find a candidate therapeutic with
9 superior efficacy to optimize standard of care,
10 and this will then become the new standard of care
11 and be included in subsequent studies with newer
12 investigational agents. There are issues around
13 that and I'm not going to get buried into that
14 right now.

15 The study population is hospitalized
16 patients with severe MERS CoV infection. I
17 mentioned how important it was to define your
18 population, define what is severe. Right now, and
19 I think this should stimulate some ethical
20 discussion, we're going to look at first or at
21 least discuss first enrolling 18 years and above.

22 There has really been a strong tradition

1 in the regulatory world to look at the studies in
2 adults first and then go to children. In the case
3 of emerging disease, you're not going to have any
4 experience with the drug, so it's easy to fall
5 into the conservative mode. I think it's
6 important to try to consider other special
7 populations, particularly if the epidemiology
8 shows the disease is severe in these special
9 populations.

10 We would like to make sure we have
11 documented MERS CoV illness at the onset of
12 recruitment with a rapid PCR. Right now, that's
13 not available. I think technology is close, that
14 maybe by the time we start, we might have the
15 ability to do that, and put a PCR 24/7 in a
16 clinical site. That would be ideal, to at least
17 have it there and be at least tested once a day.
18 Anything to identify a MERS infected patient up
19 front, I think, will avoid enrolling people who
20 don't have MERS. The final analysis will be only
21 on MERS CoV infected individuals.

22 Exclusion criteria. I think it is

1 important to keep it as simple as possible.

2 Certainly known allergy to the components of the
3 therapeutic. Right now, children or pregnant
4 children. I'm a pediatrician, so that hurts to
5 say that.

6 Any medical condition that would place
7 the patient at unreasonable risk from being in the
8 study, and then certainly any prior treatment with
9 a therapeutic agent against MERS.

10 The study endpoints. Right now, as I
11 said earlier, we are going to use mortality. I
12 must admit we are copying off Ebola, but it seems
13 to be relatively relevant, so we're going to look
14 at mortality at 28 days. As we talk with the
15 Saudi's, I think we'll learn a little bit more
16 about the epidemiology, and that number may
17 change.

18 Secondary endpoints. Dr. Neaton is in
19 the room. We are kind of excited about looking at
20 ordinal endpoints. I'm not going to go through
21 the whole story of that, but the ordinal endpoints
22 are anchored by two extremes. One is the most

1 severe, which would be death, you can't get more
2 severe than that, and then by a patient being home
3 and in normal function.

4 There are in between factors, so the
5 idea is to pick a point in time where you might
6 see a shift towards less severe disease in the
7 group that got the investigational agent over
8 standard of care.

9 Also, we want to look at safety. Right
10 now, we are thinking about measuring cumulative
11 incidence of adverse events, particularly serious
12 adverse events, by day 56 after enrollment.

13 Other secondary endpoints that may be
14 important, certainly we're hoping that phase one
15 trials would be done by our partners at NIH, to
16 look at safety and pharmacokinetics in healthy
17 people, but I think it's critical to do the same
18 thing in those who have serious disease.

19 The diagnostics, I think, is critical
20 also for looking at viral shedding and viral
21 titers. It may be hard for MERS because it has
22 been shown clinically, at least right now, the

1 best recovery of detectable virus by PCR has been
2 for lower respiratory tract samples. You can't
3 just stick a catheter down into the lungs every
4 day. I think that could be an issue. It's less
5 frequently detected in the upper respiratory
6 tract, and it may have to do with receptors. I
7 don't know.

8 Other suggestions have been tied to
9 randomization to various clinical outcomes. I'm
10 not going to go through all of them on this slide.

11 Also, at the end, and I think the
12 stories that we heard this morning particularly
13 about Ebola, we need to follow these patients long
14 term to look for relapse.

15 Just to go over this again, the simplest
16 iteration would be a two arm study where arm one
17 would be standard of care plus placebo if
18 available, and arm two would be agent X plus
19 standard of care. Then these subjects would be
20 followed, and there would be interim analysis
21 periodically. We decided tentatively to look at
22 it after the first 10 are enrolled per arm, and

1 then go after every 20, until you get to 100.

2 If agent X is significantly superior
3 than standard of care, this will become part of
4 the new standard of care for subsequent
5 investigations when new drugs come or new agents
6 come.

7 More complex iteration obviously
8 involves using multiple arms. I only put three
9 here, but that doesn't mean it has to stop at
10 three. Again, 100 per arm. Again, follow them
11 with interim analyses, and then hopefully be able
12 to identify at least one so-called winner that is
13 superior than standard of care. Then this would
14 become the standard of care for subsequent trials.

15 There are still questions about what to
16 do with multiple arms, what happens if both agent
17 X and Y are superior to standard of care. How do
18 you declare a winner? Well, you might not have to
19 declare one, but if you want to, you might want to
20 look at comparison data between the two agents and
21 see if they're superior or at least show a trend,
22 and also safety signals.

1 I think this is an important issue to
2 discuss going forward when we talk about these
3 adaptive trials.

4 Issues that I see, and I'm just a simple
5 pediatrician, we may not want to study two of the
6 same type of products in a trial if we can avoid
7 it, or if that's possible, so for example, not
8 look at two monoclonal antibodies at once, but try
9 to use a monoclonal antibody and perhaps a small
10 molecule.

11 Consider a combination of therapeutics
12 to become the new standard of care. Those of us
13 who are in infectious disease know quite well that
14 we often use multiple therapies against different
15 types of pathogens.

16 Finally, I keep hinting about this, but
17 what about the special populations, especially
18 pregnant women and children? Now, for MERS right
19 now, the epidemiology looks like for children not
20 as severe and it is certainly less frequent, so it
21 may not be as -- I don't want to say important --
22 a primary concern yet, but I think for emerging

1 infectious disease, this type of information is
2 critical to think about including children.

3 Pregnant women, I just don't know any
4 information right now on epidemiology in pregnant
5 women. One might guess because they are
6 immunosuppressed, it might be worse, but I just
7 don't know the information.

8 Other issues may come up with this
9 adaptive trial that we are not aware of yet. This
10 has really only been used right now in Ebola. I
11 think even the people who designed that recognize
12 that things may change with subsequent studies and
13 with emerging infectious pathogens.

14 I want to thank you for listening. I
15 know it's the end of the day. I hope you learned
16 something about our approach to the MERS protocol.